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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	25

Application Number	10/010,114
Filing Date	November 13, 2001
First Named Inventor	R. Boutin
Art Unit	1632
Examiner Name	D. Crouch
Attorney Docket Number	AHP1CUSA

ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
  - [✓] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [✓] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

Customer No. 38199
Express Mail No. ED227893948US

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HOWSON AND HOWSON		
Signature	Cathy A Kodroff		
Printed name	Cathy A. Kodroff		
Date	June 29, 2005	Reg. No.	33,980

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Effective on 12/08/2004.
Fees Pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)	500.00

Complete if Known	
Application Number	10/010,114
Filing Date	November 13, 2001
First Named Inventor	R. Boutin
Examiner Name	D. Crouch
Art Unit	1632
Attorney Docket No.	AHP1CUSA

METHOD OF PAYMENT (check all that apply)

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims _____ - 20 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims _____ - 3 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = _____ Extra Sheets / 50 = _____ Number of each additional 50 or fraction thereof (round up to a whole number) x Fee ($) _____ = Fee Paid ($) _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Reply Brief fee	500

SUBMITTED BY

Signature	Cathy A. Kodroff	Registration No. (Attorney/Agent) 33,980	Telephone 215-540-9200
Name (Print/Type)	Cathy A. Kodroff		Date June 29, 2005

06-30-05

AR

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	:	10/010,114	Confirmation No. 5743
Applicant	:	Raymond H. Boutin	
Filed	:	November 13, 2001	
TC/A.U.	:	1632	
Examiner	:	D. Crouch	
Docket No.	:	AHP1CUSA	
Customer No.	:	38199	

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22323-1450

REPLY BRIEF

Sir:

This Reply Brief is timely filed in response to the Examiner's Answer mailed May 3, 2005. Applicant presents this Reply in order to correct an error noted in the examiner's recitation of the Art of Record at page 3 of the Examiner's Answer.

The fee of $500.00 for filing this Reply Brief is attached hereto. The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper, or credit any overpayment, to our Deposit Account, No. 08-3040.

I. Real party in interest

A statement identifying the real party in interest is contained in the Appeal Brief, filed February 17, 2005.

II. Related appeals and interferences

None.

Express Mail No. ED227893948US

III. Status of claims

A statement identifying the status of claims is contained in the Appeal Brief, filed February 17, 2005.

IV. Status of amendments

There are no outstanding amendments.

V. Summary of claimed subject matter

A summary of the claimed subject matter is contained in the Appeal Brief, filed February 17, 2005.

VI. Grounds of rejection to be reviewed on appeal

A statement identifying the issue on appeal is contained in the Appeal Brief, filed February 17, 2005.

VII. Argument

Applicant's argument regarding the issue on appeal is contained in the Appeal Brief, filed February 17, 2005, and will not be repeated here. By way of this Reply Brief, Applicant only addresses matters raised by the Examiner's Answer ("Answer").

A. The examiner is improperly relying on Applicant's election of group I[1] in requiring that a therapeutic effect be demonstrated.

> The examiner asserts that based on the election of group I, *i.e.*, claim 3 drawn to a method for transfer to cells of a multifunctional molecular complex comprising a nucleic acid encoding a therapeutic agent,

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[1] Page 2, Office Action dated 08/13/03; and Page 1, Applicant's Response filed September 11, 2003.

> Applicant must demonstrate a therapeutic effect to support enablement of the claims.

Applicant respectfully disagrees. The examiner asserted in the restriction requirement issued in the present application[2] that the application contained fourteen unrelated inventions. However, claims 1-2, 4-9, and 17-48 were found to link the inventions. Accordingly, the linking claims were to be examined, with the restriction requirement "*subject to* the nonallowance of the linking claim(s)" (emphasis added).[3]

The examiner has failed to examine the linking claims independent of Applicant's election. Claim 1, provides:

> A method for the transfer of a nucleic acid to cells, comprising the step of introducing a multifunctional molecular complex into cells, wherein said multifunctional molecular complex comprises . . .; wherein said multifunctional molecular complex transfers said nucleic acid composition to said cells.

Thus, the question of enablement[4] is not whether a therapeutic effect is achieved in a cell following transfer according to the invention, but whether a nucleic acid is transferred to a cell by a multifunctional molecular complex according to the invention. As the claim is a transfer method and not a therapeutic method, no therapeutic effect need be demonstrated in order to support its enablement.

The examiner has acknowledged that the specification is "enabling for methods for the transfer of a nucleic acid composition to cells in culture comprising introducing a multifunctional molecular complex to cells where the complex comprises a nucleic acid encoding a therapeutic protein or polypeptide and a transfer moiety".[5] Further, Applicant

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2 Office Action dated 08/13/03.

3 *Id.* at p. 2, line 3.

4 See p. 4 of Appeal Brief, dated 02/17/05, *citing* In re Wright and MPEP 2164.04.

5 Page 2, Office Action dated 09/22/04.

has demonstrated via an unrebutted Declaration that the method is enabled for *in vivo* transfer of a nucleic acid.[6]

Applicant submits that the examiner has improperly examined the linking claims directed to methods of transfer, *e.g.*, claim 1, by requiring that a therapeutic effect be demonstrated. For the reasons set forth above, Applicant submits that the pending claims are enabled.

B. General teachings in the art of gene therapy are not appropriate guidance regarding the "state of the art" with respect to the invention of group I, i.e., claim 3 drawn to a method for transfer to cells of a multifunctional molecular complex comprising a nucleic acid encoding a therapeutic agent.

> The examiner asserts at pages 8-9 (carryover sentence) of the Answer that since the claims are directed to therapeutic agents, the art of gene therapy at the time of filing is an appropriate summary of the state of the pertinent art.

Applicant respectfully disagrees. The invention of group I, to which the examiner refers, is drawn to a method whereby a nucleic acid encoding a therapeutic agent is delivered to a cell. None of the documents on which the examiner relies for the "state of the art"[7] require that the term "introducing" of a nucleic acid in a claim be interpreted as gene therapy and preclude interpreting the claim to mean delivery of vaccinal or other therapeutic molecules (which do not constitute gene therapy). Accordingly, the art of "gene therapy" as of the filing date is not an appropriate summary of the pertinent art with respect to methods of transferring a nucleic acid to a cell.

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6 Declaration, signed 11/24/98, submitted along with Applicant's 03/05/04 Response to the Office Action dated 12/08/03.

7 See Examiner's Answer, "(9) Art of Record", p. 2-3; See also section VII. C. herein regarding correction of Anderson citation.

C. At page 3 of the Answer, the examiner incorrectly indicates that the fourth document listed ("Anderson") has the following citation: "Anderson, W.F. Gene Therapy. Scientific American. September 1995, pp. 124-128."

The examiner's remarks at page 5, lines 3-6 of the Answer are identical to those made at page 4, lines 2-5 regarding Anderson, W.F., Gene Therapy for Genetic Diseases, Human Gene Therapy, vol. 5, pp. 281-282 (1994). Further, the Anderson citation at page 5, lines 3-6 of the Answer refers to page 281, which is outside of the range listed in the citation of Anderson found in the Art of Record section of the Answer. Accordingly, it is clear that the Anderson citation presented in the Art of Record section of the Answer is incorrect.

Based on the above, Applicant requests that the record be clarified to reflect that the Anderson document of record has the following citation:

> Anderson, W.F., Gene Therapy for Genetic Diseases, Human Gene Therapy, vol. 5, pp. 281-282 (1994).

In view of Applicant's remarks herein and in the Appeal Brief, reversal of the examiner's rejection of the claims under appeal (claims 1-2, 5-9 and 17-52) is requested.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Applicants

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Claims Appendix

Claim 1(Original): A method for the transfer of a nucleic acid composition to cells, comprising the step of introducing a multifunctional molecular complex into cells,

wherein said multifunctional molecular complex comprises:

A) a nucleic acid composition; and

B) a transfer moiety comprising

(i) one or more cationic polyamine components, wherein each cationic polyamine is non-covalently bound to said nucleic acid composition and comprises from three to twelve nitrogen atoms; and

(ii) one or more endosome membrane disruption promoting components attached to at least one nitrogen atom of at least one of said polyamine components through an alkyl, carboxamide, carbamate, thiocarbamate, or carbamoyl bridging group, said one or more endosome membrane disruption promoting components independently selected from (a) at least one lipophilic long chain alkyl group or (b) a fusogenic peptide, cholic acid or cholesteryl group or a derivative thereof;

wherein said multifunctional molecular complex transfers said nucleic acid composition to said cells.

Claim 2(Original): A method according to Claim 1 wherein said nucleic acid composition is a nucleic acid molecule that comprises a nucleotide sequence that encodes a peptide or protein, or serves as a template for a nucleic acid molecule.

Claim 3(Withdrawn): A method according to Claim 2 wherein the peptide, protein or nucleic acid molecule is selected from the group consisting of vaccines; foodstuffs and nutritional supplements; compounds of agricultural significance; herbicides and plant growth regulants; insecticides; miticides; rodenticides; and fungicides; compounds useful in animal health; parasiticides; nematocides.

Claim 4(Original): A method according to Claim 1 wherein the target cells are cultures of host cells comprising microorganism cells of bacteria, yeast, plant or mammalian cells; said cell cultures being maintained in accordance with fermentation techniques which maximize production of the peptide, protein or functional nucleic acid molecule being produced.

Claim 5(Original): A method according to Claim 1 wherein the nucleic acid composition comprises a nucleotide sequence that encodes a protein and is operably linked to regulatory sequences.

Claim 6(Original): A method according to Claim 1 wherein the nucleic acid composition comprises a nucleotide sequence that encodes a protein which comprises at least one epitope that is identical or substantially similar to an epitope of an antigen against which an immune response is desired, said nucleotide sequence being operably linked to regulatory sequences.

Claim 7(Original): The method according to claim 1, wherein the transfer moiety of said multifunctional molecular complex further comprises at least one receptor specific binding component which is a ligand for a receptor on a target cell.

Claim 8(Original): The method according to claim 1, wherein the cationic polyamine comprises the formula (1):

$$NR(R^3)\text{-}[\text{-}(CR^1R^2)_m\text{-}N(R^3)\text{-}]_n\text{-}(CR^1R^2)_m\text{-}NR(R^3) \quad (1)$$

wherein:

R, R^1 and R^2 are each independently selected from the group consisting of hydrogen and $C_{1\text{-}6}$ alkyl;

m in each occurrence is independently selected from the integers 2 through 5 inclusive;

n is selected from the integers 1 through 10 inclusive; and

R^3 is independently selected from the group consisting of hydrogen; C_{1-6} alkyl, an endosome membrane disruption promoting component, and a receptor specific binding component, or $NR(R^3)$ is guanidino,

wherein said transfer moiety comprises at least one endosome membrane disruption promoting component attached to at least one nitrogen atom of at least one of said cationic polyamine components.

Claim 9(Original): The method according to claim 1, wherein the nucleic acid composition is a plasmid.

Claims 10-16. Cancelled.

Claim 17(Original): The method according to claim 7, wherein the receptor specific binding component is attached through a bridging group to either (i) to a further nitrogen atom of at least one of said cationic polyamine components to which said one or more endosome membrane disruption promoting components is attached, or (ii) to a nitrogen atom of at least one further polyamine component which does not have attached thereto any endosome membrane disruption promoting component.

Claim 18(Original): The method according to claim 17, wherein the bridging group through which the receptor specific binding component is attached is selected from the group consisting of an alkyl, carboxamide, carbamate, thiocarbamate, and carbamoyl bridging group.

Claim 19(Original): The method according to claim 8, wherein said one or more endosome membrane disruption promoting components are independently selected from the group consisting of:

(a) $-B-(CR^1R^2)_j-C(R)_3$, where R is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, or $C(R)_3$ is C_6H_5 aromatic or absent; R^1 and R^2 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; j is an integer from 0 to 24 inclusive; and B is optionally absent, or is a bridging group of the formula:

(i) $-(CR^1R^2)_k-C(=O)-Z-$;

(ii) $-(CR^1R^2)_k-N(R)-C(=O)-Z-$;

(iii) $-(CR^1R^2)_k-N(R)-\{-C(=O)-CH_2-O-[-(CH_2)_2-O-]_l-(CH_2)_k-N(R)\}_p-C(=O)-Z-$; or

(iv) $-(CR^1R^2)_k-C(=O)-\{-N(R)-[-(CH_2)_2-O-]_l-CH_2-C(=O)\}_p-Z-$;

where k is, independently, an integer from 1 to 11 inclusive, 1 is an integer from 0 to 30 inclusive, and p is an integer from 1 to 3 inclusive; R is independently defined as above or is absent, R^1 and R^2 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; and Z is O, OH, S, N(R), or is absent;

(b) $-B-(R^4)R$, where R, R^1 and R^2 are each independently defined as above; B cannot be absent and is a bridging group independently selected from groups (i) through (iv) above, and additionally from the group of the formula:

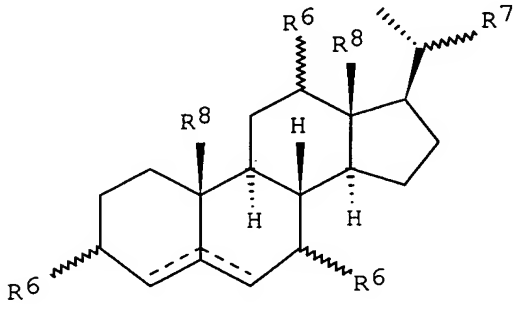
(v) $-(CR^1R^2)_{j=}-X-$, where j= is an integer from 1 to 8 inclusive; R^1 and R^2 are each independently defined as above;

X is O, S, N(R), or absent; and

R^4 is independently selected from the group consisting of:

(i) fusogenic peptides comprising spike glycoproteins of enveloped animal viruses;

(ii) cholic acid derivatives of the formula (2):



(2)

where:

~~www~~ represents a bond of unspecified stereochemistry;

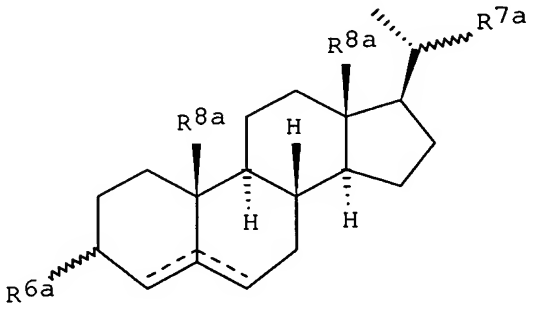
--- represents a single or double bond, forming a saturated or unsaturated portion of the ring system, provided that they cannot both be unsaturated at the same time, whereby the ring system must be either Δ4 or Δ5;

R^6 is -H, -OH, $-CO_2H$, $-C(=O)NH_2$, $-OC(=O)NH_2$, $-NH_2$, or $-O(CH_2CH_2O)_{n=}H$, where n= is an integer from 1 to 6 inclusive;

R^7 is a radical that forms the point of attachment of the cholic acid derivative, comprising $-C_{1-6}$ alkyl- or $-C_{1-6}$ alkylcarbonyl-; and

R^8 is C_{1-6} alkyl; and

(iii) cholesteryl derivatives of the formula (3):



(3)

where:

~~www~~ represents a bond of unspecified stereochemistry;

--- represents a single or double bond, forming a saturated or unsaturated portion of the ring system, provided that they cannot both be unsaturated at the same time, whereby the ring system must be either Δ4 or Δ5;

R^{6a} is a radical that forms the point of attachment of the cholesteryl derivative, comprising -C_{1-6} alkyl-, -OC(=O)-, or -OCH_2C(=O)-;

R^{7a} is C_{1-6} alkyl; and

R^{8a} is C_{1-6} alkyl.

Claim 20(Original): The method according to claim 8, wherein R^3 has the formula:

-B-(R^5)-R, where B cannot be absent and is a bridging group independently selected from groups (i) through (v) inclusive; R is independently as defined or absent; and R^5 is a receptor specific binding component independently selected from the group consisting of:

(i) D-biotin;

(ii) β-3'-propionyl galactosyl-β1-4- thioglucoside;

(iii) N^2, N^6-bis(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysine;

(iv) N^2, N^6-bis(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysyl-N^6-(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysine;

(v) 5-methyltetrahydrofolate;

(vi) folic acid;

(vii) folinic acid;

(viii) α-3'-propionyl thiomannoside;

(ix) α-3'-propionyl thiomannoside-6-phosphate; and

(x) an antibody which binds specifically to a cell membrane protein.

Claim 21(Original): The method according to claim 8, wherein the cationic polyamine has the formula: NH_2-$(CH_2)_3$-$N(R^3)$-$(CH_2)_4$-NH_2.

Claim 22(Original): The method according to claim 21 wherein R^3 is an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$, wherein $C(R)_3$ is C_6H_5 aromatic; R^1 and R^2 are each hydrogen; j is 1; and B is a bridging group of the formula: -$(CR^1R^2)_k$-C(=O)-Z-, wherein k is 5; and Z is O.

Claim 23(Original): The method according to claim 21 wherein R^3 is an endosome membrane disruption promoting component of the formula -B-(R^4)R, wherein B is a bridging group of the formula: -$(CR^1R^2)_k$-C(=O)-Z-; R is absent, R^1 and R^2 are each hydrogen; k is 5, Z is absent; and R^4 is a fusogenic peptide.

Claim 24(Original): The method according to claim 21 wherein R^3 is an endosome membrane disruption promoting component of the formula -B-(R^4)R, wherein B is a bridging group of the formula: -$(CR^1R^2)_{j=}$-X-; R is absent, R^1 and R^2 are each hydrogen; j= is 5, X is N(R); and R^4 is a cholic acid derivative wherein R^6 is OH, R^7 is C_3 alkylcarbonyl and R^8 is C_1 alkyl.

Claim 25(Original): The method according to claim 21 wherein R^3 is an endosome membrane disruption promoting component of the formula -B-(R^5)R, wherein R is absent and B is a bridging group of the formula: -(CR^1R^2)$_k$-N(R)-C(=O)-Z- in which R, R^1 and R^2 are each hydrogen; k is 5, Z is absent; and R^5 is α-3'-propionyl thiomannoside.

Claim 26(Original): The method according to claim 21 wherein R^3 is an endosome membrane disruption promoting component of the formula -B-(CR^1R^2)$_j$-C(R)$_3$, wherein C(R)$_3$ is C_6H_5 aromatic; R^1 and R^2 are each hydrogen; j is 1 and B is a bridging group of the formula: -(CR^1R^2)$_k$-N(R)-C(=O)-Z-; k is 5, N(R) is NH and Z is O.

Claim 27(Original): The method according to claim 8, wherein the cationic polyamine has the formula NH(R^{30})-(CH_2)$_3$-N(R^3)-(CH_2)$_4$-N(R^3)-(CH_2)$_3$-NH(R^{30})
wherein:

R^{30} is hydrogen or NH(R^{30}) is guanidino;

at least one R^3 is an endosome membrane disruption promoting component of the formula -B-(CR^1R^2)$_j$-C(R)$_3$.

Claim 28(Original): The method according to claim 27 wherein:

R^{30} is hydrogen; and

each R^3 is an endosome membrane disruption promoting component of the formula -B-(CR^1R^2)$_j$-C(R)$_3$,

wherein C(R)$_3$ is C_6H_5 aromatic; R^1 and R^2 are each hydrogen; j is 1; and B is a bridging group of the formula: -(CR^1R^2)$_k$-N(R)-C(=O)-Z-;

where k is 5; N(R) is NH; and Z is O.

Claim 29(Original): The method according to claim 27 wherein:

R^{30} is hydrogen; and

each R^3 is an endosome membrane disruption promoting component of the formula $-B-(CR^1R^2)_j-C(R)_3$,

wherein B is absent, R, R^1 and R^2 are each hydrogen; and j is 7.

Claim 30(Original): The method according to claim 27 wherein:

$NH(R^{30})$ is guanidino; and

each R^3 is an endosome membrane disruption promoting component of the formula $-B-(CR^1R^2)_j-C(R)_3$,

wherein B is absent, R, R^1 and R^2 are each hydrogen; and j is 7.

Claim 31(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

one R^3 is hydrogen; and

one R^3 is an endosome membrane disruption promoting component of the formula $-B-(R^4)-R$,

wherein R is absent and B is a bridging group of the formula:

$-(CR^1R^2)_{j=}-X-$, in which R, R^1 and R^2 are each hydrogen; j= is 5; and X is N(R) and

where R^4 is a type (iii) cholesteryl derivative of formula (3):

R^{6a} is O-C(=O)- and a point of attachment of cholesteryl derivative;

R^{7a} is C_5 alkyl; and

R^{8a} is C_1 alkyl.

Claim 32(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

each R^3 is an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$,

wherein B is a bridging group of the formula: -$(CR^1R^2)_k$-C(=O)-Z-; R^1 and R^2 are each hydrogen; j is 0, k is 11; Z is N(R) where R is C_1 alkyl and $C(R)_3$ is CH_3.

Claim 33(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

each R^3 is an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$;

wherein B is a bridging group of the formula: -$(CR^1R^2)_k$-C(=O)-Z-; R^1 and R^2 are each hydrogen; j is 1, k is 11; Z is O and $C(R)_3$ is C_6H_5 aromatic.

Claim 34(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

each R^3 is an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$;

wherein B is a bridging group of the formula: -$(CR^1R^2)_k$-C(=O)-Z-; R^1 and R^2 are each hydrogen; j is 0, k is 11; Z is OH and $C(R)_3$ is absent.

Claim 35(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

one R^3 is hydrogen; and

one R^3 is an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$;

wherein B is a bridging group of the formula: $-(CR^1R^2)_k-C(=O)-Z-$; R^1 and R^2 are each hydrogen; j is 1, k is 11; Z is O and $C(R)_3$ is C_6H_5 aromatic.

Claim 36(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

one R^3 is hydrogen; and

one R^3 is an endosome membrane disruption promoting component of the formula $-B-(CR^1R^2)_j-C(R)_3$;

wherein B is a bridging group of the formula: $-(CR^1R^2)_k-C(=O)-Z-$; R^1 and R^2 are each hydrogen; j is 0, k is 11; Z is OH and $C(R)_3$ is absent.

Claim 37(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

each R^3 is an endosome membrane disruption promoting component of the formula $-B-(R^5)R$;

wherein R is absent and B is a bridging group of the formula: $-(CR^1R^2)_k-N(R)-C(=O)-Z-$, in which R, R^1 and R^2 are each hydrogen; k is 5; Z is absent and

R^5 is α-3'-propionyl thiomannoside.

Claim 38(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

one R^3 is hydrogen; and

one R^3 is an endosome membrane disruption promoting component of the formula $-B-(R^5)R$;

wherein R is absent and B is a bridging group of the formula: $-(CR^1R^2)_k-N(R)-\{-(C=O)-CH_2-O-[-(CH_2)_2-O-]_l-(CH_2)_k-N(R)\}_p-C(=O)-Z-$ in which R, R^1 and R^2 are each hydrogen; k is 5; l is 5; p is 1; Z is absent; and

R^5 is α-3'-propionyl thiomannoside.

Claim 39(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

one R^3 is hydrogen; and

one R^3 is an endosome membrane disruption promoting component of the formula $-B-(R^5)R$;

wherein R is absent and B is a bridging group of the formula: $-(CR^1R^2)_k-N(R)-\{-(C=O)-CH_2-O-[-(CH_2)_2-O-]_l-(CH_2)_k-N(R)\}_p-C(=O)-Z-$ in which R, R^1 and R^2 are each hydrogen; k is 5; l is 20; p is 1; Z is absent; and

R^5 is α-3'-propionyl thiomannoside.

Claim 40(Original): The method according to claim 27 wherein:

R^{30} is hydrogen;

one R^3 is hydrogen; and

one R^3 is an endosome membrane disruption promoting component of the formula $-B-(R^5)R$;

wherein R is absent and B is a bridging group of the formula: $-(CR^1R^2)_k-N(R)-\{-(C=O)-CH_2-O-[-(CH_2)_2-O-]_l-(CH_2)_k-N(R)\}_p-C(=O)-Z-$ in which R, R^1 and R^2 are each hydrogen; k is 5; l is 5; p is 1; Z is absent; and

R^5 is N^2, N^6-bis(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysyl-N^6-(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysine.

Claim 41(Original): The method according to claim 8, wherein said transfer moiety comprises more than one cationic polyamine component.

Claim 42(Original): The method according to claim 8, wherein a first cationic polyamine component comprises an endosome membrane disruption promoting component and a second cationic polyamine component comprises a receptor specific binding component.

Claim 43(Original): The method according to claim 42, wherein the first cationic polyamine component has an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$, wherein $C(R)_3$ is absent, R^1 and R^2 are each hydrogen; j is 0 and B is a bridging group selected from the group consisting of (i), (ii), (iii) and (iv).

Claim 44(Original): The method according to claim 42, wherein the first cationic polyamine component has an endosome membrane disruption promoting component of the formula -B-$(CR^1R^2)_j$-$C(R)_3$, wherein $C(R)_3$ is absent, R^1 and R^2 are each hydrogen; j is 0 and B is a bridging group of the formula: -$(CR^1R^2)_k$-C(=O)-Z-; k is 11 and Z is OH.

Claim 45(Original): The method according to claim 42, wherein the first cationic polyamine component has an endosome membrane disruption promoting component of the formula -B-(R^4)R, wherein R^4 is a cholesteryl derivative.

Claim 46(Original): The method according to claim 42, wherein the first cationic polyamine component has an endosome membrane disruption promoting component of the formula -B-(R^4)R, wherein R is a absent and B is a bridging group of the formula: -$(CR^1R^2)_{j=}$-X-, in which R, R^1 and R^2 are each hydrogen; j= is 5; and X is N(R) and where R^4 is a type (iii) cholesteryl derivative of formula (3): R^{6a} is O-C(=O)- and a point of attachment of cholesteryl derivative; R^{7a} is C_5 alkyl; and R^{8a} is C_1 alkyl.

Claim 47(Original): The method according to claim 42, wherein the receptor specific binding component of said second cationic polyamine component is selected from the group consisting of:

β-3= propionyl galactosyl-β1-4-thioglucoside;

N^2, N^6-bis(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysine;

N^2, N^6-bis(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysyl-N^6-(β-3'-propionyl galactosyl-β1-4-thioglucoside)lysine;

α-3'-propionyl thiomannoside; and

α-3'-propionyl thiomannoside-6-phosphate.

Claim 48(Original): A method for delivering a nucleic acid molecule to a targeted population of cells of an individual, said method comprising the step of delivering to the individual a multifunctional molecular complex comprising:

A) a nucleic acid molecule; and

B) a transfer moiety comprising one or more cationic polyamine components, wherein each cationic polyamine is non-covalently bound to said nucleic acid molecule and each independently comprises a cationic polyamine of the formula (1):

$$NR(R^3)\text{-}[\text{-}(CR^1R^2)_m\text{-}N(R^3)\text{-}]_n\text{-}(CR^1R^2)_m\text{-}NR(R^3) \quad (1)$$

wherein:

R, R^1 and R^2 are each independently selected from the group consisting of hydrogen and $C_{1\text{-}6}$ alkyl;

m in each occurrence is independently selected from the integers 2 through 5 inclusive;

n is selected from the integers 1 through 10 inclusive;

R^3 is independently selected from the group consisting of hydrogen; C_{1-6} alkyl, and an endosome membrane disruption promoting component, or $NR(R^3)$ is guanidino;

wherein said transfer moiety comprises at least one endosome membrane disruption promoting component attached to at least one nitrogen atom of at least one of said cationic polyamine components;

wherein said transfer moiety comprises at least one receptor specific binding component attached either (i) to a further nitrogen atom of at least one of said cationic polyamine components to which said one or more endosome membrane disruption promoting components is attached, or (ii) to a nitrogen atom of at least one further polyamine component which does not have attached thereto any endosome membrane disruption promoting component,

wherein said receptor specific binding component which is a ligand for natural receptors of said target cells.

Claim 49 (New): A method according to Claim 2 wherein the peptide, protein or nucleic acid molecule is a therapeutic agent.

Claim 50 (New): A method for the transfer of a nucleic acid composition to cells, comprising the step of introducing a multifunctional molecular complex into cells, wherein said multifunctional molecular complex comprises:

(a) a nucleic acid molecule; and

(b) a transfer moiety comprising:

(i) one or more cationic polyamine components, wherein each cationic polyamine is non-covalently bound to a nucleic acid composition and comprises from three to twelve nitrogen atoms; and

(ii) one or more endosome membrane disruption promoting components independently selected from the group consisting of:

(a) at least one lipophilic long chain alkyl group attached to a nitrogen atom of said polyamine,

(b) a fusogenic peptide attached to a nitrogen atom of said polyamine through a short alkyl bridging group having a terminal carboxyl, amino, hydroxyl or sulfhydryl group, and

(c) a cholic acid or cholesteryl or a derivative thereof attached to a nitrogen atom of said polyamine through a short alkyl bridging group having a terminal carboxyl, amino, hydroxyl or sulfhydryl group,

wherein said multifunctional molecular complex transfers said nucleic acid composition to said cells.

Claim 51 (New): The method according to claim 50, wherein said transfer moiety further comprises at least one receptor specific binding component which is a ligand for a receptor on a target cell.

Claim 52 (New): The method according to claim 50, wherein the receptor specific binding component is attached through a bridging group to either (i) to a further nitrogen atom of at least one of said cationic polyamine components to which said one or more endosome membrane disruption promoting components is attached, or (ii) to a nitrogen atom of at least one further polyamine component which does not have attached thereto any endosome membrane disruption promoting component.

(IX) Evidence Appendix

An evidence appendix is contained in the Appeal Brief, filed February 17, 2005.

(X) Related Proceedings Appendix

None applicable.